INCIDENCE OF REJECTION, MORBIDITY, MORTALITY AND GRAFT FUNCTION IN RENAL TRANSPLANT RECIPIENTS FOLLOWING CYCLOSPORINE TO AZATHIOPRINE SWITCH

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by

Laurie-Ann Nessralla

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ABSTRACT

INCIDENCE OF REJECTION, MORBIDITY, MORTALITY AND GRAFT FUNCTION IN RENAL TRANSPLANT RECIPIENTS FOLLOWING CYCLOSPORINE TO AZATHIOPRINE SWITCH. Laurie-Ann Nessralla, Margaret J. Bia, M.D., Section of Nephrology, Department of Internal Medicine, Yale University, School of Medicine, New Haven, CT.

Cyclosporine and azathioprine are immunosuppressive agents used in the treatment of kidney graft recipients. Cyclosporine interferes with the production of lymphokines Interleukin-1 and Interleukin-2. Azathioprine interferes with the process of blastogenesis of T-lymphocyte clones. Cyclosporine has been shown to be a superior immunosuppressive agent when compared to azathioprine. It has also been shown, however, that cyclosporine also causes a rise in serum creatinine concentration values, a reduction in the glomerular filtration rate, tubular injury, interstitial fibrosis, hirsutism, liver disease, hypertension and gastrointestinal symptomatology. Side effects such as these cause one to question whether cyclosporine should be used in conjunction with prednisone as the sole immunosuppressive post-transplantation, or should a switch to azathioprine-prednisone occur. In cases

of renal and non-renal toxicity, a switch to azathioprine-prednisone should occur.

It had been the policy of Yale-New Haven Hospital between December 1983 to July 1986 to switch renal transplant patients from cyclosporine-prednisone to azathioprine-prednisone immunosuppressive treatment between 3-21 months post-transplantation to prevent side effects such as those mentioned above. The present investigation was performed to evaluate the clinical course of 24 such cadaveric renal transplant patients that underwent this switch therapy to investigate the incidence of acute allograft rejection following the switch as well as renal function and graft survival at 6, 12, 18, 24, 30, 36 and >36 months post-transplantation.

Results indicate that 42% of patients investigated experienced a rejection post-switch which was usually mild. Although rejections were usually mild, 3 patients experiencing a rejection post-switch eventually lost their grafts. Factors such as age, sex, race, presence of diabetes mellitus, the presence of a rejection before the switch, time of switch post-transplantation, and renal function before the switch were investigated and found to have no association with an increased frequency of rejection post-switch. Improvement in renal function was especially evident in those patients who did not suffer a rejection post-switch. Thus, it is seen that an immunosuppressive switch cannot be undertaken without caution.

INTRODUCTION

Cyclosporine and azathioprine are immunosuppressive agents used in the treatment of kidney graft recipients. Cyclosporine is a fungal polypeptide which inhibits T-cell proliferation. Cyclosporine also interferes with the production of lymphokines such as Interleukin-1 and Interleukin-2. Azathioprine, an imidazole derivative, prevents the expansion of T-lymphocyte clones in their response to foreign antigens by interfering with blastogenesis. Both cyclosporine and azathioprine are used as potent immunosuppressive agents following various transplant procedures. When considering kidney allograft recipients, there is a risk of nephrotoxicity, renal scarring, and a high cost factor associated with the long-term use of cyclosporine.[1] It had been the policy of Yale-New Haven Hospital from December 1983 to March 1986 to switch kidney graft recipients from cyclosporine-prednisone to azathioprine-prednisone immunosuppressive treatment at 3-21 months post-transplant to avoid the nephrotoxicity of cyclosporine.

In examining cyclosporine and azathioprine more closely, cyclosporine has been shown to be a more potent and effective immunosuppressive agent following transplantation procedures. The mechanism of action of cyclosporine is controversial but has been extensively investigated.

Ferguson et. al monitored the immunosuppressive effect of cyclosporine by assaying the proliferative responses of both patient and normal lymphocytes cultured in the presence of patient plasma obtained at various intervals following an oral dose of cyclosporine.[2] Results indicated that initially cyclosporine exhibited extensive immunosuppressive effects which correlated with a rapid increase in cyclosporine levels detected in the peripheral blood.[2] Inhibition of lymphocyte proliferation, however, continued despite an increased time period post-dose of cyclosporine. This demonstrated the presence of decreased lymphocyte activity and therefore immunosuppressive characteristics following a single oral dose of cyclosporine.[2]

Lafferty et. al have proposed two different models concerning the site of action of cyclosporine.[3] The first model, the subset model, suggests that different populations of T-lymphocytes exhibit different sensitivities to cyclosporine. T-helper and T-cytotoxic lymphocytes are primarily affected by cyclosporine, while T-suppressor cells remain unaffected. The T-helper cells are thought to be the main site of action of cyclosporine, due their necessity in the activation of the cytotoxic subset which is therefore indirectly affected by cyclosporine.[4,2] The second model, the signaling model, postulates that cyclosporine interferes with the transmission of the antigen specific signal to the cell interior at some stage following antigen binding.[5,6] It has been experimentally found, however, that cyclosporine

does not inhibit antigen binding, the synthesis of lymphokines within the cell, or the export of the lymphokines from the cell.[2] Thus, cyclosporine interferes with the transmission of the antigenic signal to the nucleus of the cell which as a consequence interferes with Interleukin-1 and Interleukin-2 production by the T-helper cells.[7] Later, Cohen et. al reported that one year graft survival rates in those renal graft recipients using cyclosporine alone was 70-80%, and cyclosporine was thus a successful and effective immunosuppressive agent.[8] In summary, cyclosporine exerts its main effect upon immunosuppression through selectively inhibiting T-helper cell production of Interleukin-1 and Interleukin-2 growth factors that are essential for B-cell and cytotoxic T-cell differentiation and proliferation, while permitting the expansion of suppressor T-cells.[7] It is clear from the evidence presented that cyclosporine has a very different mechanism of action when compared to azathioprine which has its main effect in blastogenesis. Azathioprine exerts its main effect via its metabolism effects. Azathioprine is metabolized in the liver to 6-mercaptopurine which interferes with normal purine metabolism and thus DNA synthesis and cell proliferation.[9] It has, however, been proven that cyclosporine is toxic to the kidney and produces renal scarring which is inevitably accompanied by deteriorating renal function.[1] Myers et. al evaluated glomerular filtration in 17 recipients of heart transplants

who were treated for twelve months or longer with cyclosporine. The control group was made up of 15 heart-transplant recipients who were treated with azathioprine and who had also survived for at least 12 months. Serum creatinine concentrations were similar in the two groups at the time of transplantation, but these levels rose from 1.3±0.1mg/dL to 2.1±0.2mg/dL in the cyclosporine group and declined from 1.3±0.1mg/dL to 1.0±0.4mg/dL in the azathioprine control group at one year post-transplantation.[1] This rise in the serum creatinine concentration in the cyclosporine group was accompanied by a 50 percent reduction in the glomerular filtration rate, a slight impairment of both proximal and distal tubular function, and a histopathological demonstration of atrophic tubular injury accompanied by interstitial fibrosis.[1] These events were not experienced in the azathioprine treated control group. Two patients in the cyclosporine treatment group developed end-stage renal failure requiring dialysis. It was thus concluded that long term cyclosporine therapy is associated with irreversible and potentially progressive nephropathy.[1] Myers et. al conducted this study on heart transplant recipients which illustrated the destructive effects of cyclosporine on the intact kidneys of these patients, and thus forms a basis for concern regarding such destructive effects on the kidney in renal transplant recipients.

Similar reports concerning nephrotoxicity associated

with long-term cyclosporine use have been documented in renal transplant patients. Hunsicker has reported the results from five United States transplant centers and one Canadian center which used cyclosporine-prednisone in the treatment of kidney transplant recipients before this drug was released for universal use.[10] Thus, these centers are able to report the minimum of a two year follow up time describing the long-term effects of cyclosporine treatment. Hunsicker reports that graft survival in recipients of first transplants treated with cyclosporine to be 7-9% better at all time intervals following transplantation.[10] Four out of five U.S. centers and the Canadian center reported a one year patient survival of 92-96% of patients treated with cyclosporine-prednisone. One year graft survival was reported as 73%$\pm$2%, which was a gain of 25-30% over conventional azathioprine-prednisone immunosuppression.[10] Hunsicker concluded that cyclosporine treatment following renal transplantation will improve the survival of first cadaveric renal grafts by 10% at one year.[10] This statement, however, is debated by the Minnesota Trial Group.[11] The Minnesota Trial Group reported that the advantage seen in graft survival by the six centers initially using cyclosporine was lost by three years post-transplantation.[11] The Minnesota randomized trial involved 131 patients in the cyclosporine-prednisone group. In this group, 19% of patients were switched to azathioprine-prednisone treatment, and 35% had azathioprine

added to their immunosuppressive regimen with a concomitant lowering of the cyclosporine dose because of nephrotoxicity.[11] Thus, this group concluded that cyclosporine should be used in most renal allograft recipients in combination with azathioprine in order that a lower dose of cyclosporine can be employed and side effects of cyclosporine minimized.

The risk of nephrotoxicity, possible renal scarring, hirsutism, hypertension, liver disease and gastrointestinal symptomatology associated with cyclosporine use, raises questions addressing whether it should be the sole immunosuppressive used in conjunction with prednisone post-transplantation, or whether a switch to azathioprine and prednisone should occur. In cases of renal toxicity as indicated from elevated serum creatinine concentrations, and non-renal toxicity, a switch to azathioprine-prednisone treatment is often considered. Gonwa et. al have demonstrated that patients other than primary cadaveric transplants with stable renal function (i.e. defined as serum creatinine concentrations less than 2mg/dL), switched to azathioprine-prednisolone at an average of 7.97 months post-transplantation, had severe problems of graft loss post-switch.[12] Those patients who were retransplants, those who exhibited prolonged poor renal function post-transplantation, or those who were classified as non-responsive rejection patients were problematic post-switch.

The immunosuppressive conversion resulted in graft loss in these patients and sometimes patient loss.[9]

Similar results were obtained from Rocher et. al who switched 10 patients at 50 days post-transplantation and 19 patients at 8 months post-transplantation from treatment with cyclosporine to azathioprine.[13] All patients had a creatinine greater than 2mg/dL before conversion which decreased post-conversion.[13] A beneficial creatinine response, however, was accompanied by a 22% graft loss post-switch in the patients switched at 8 months post-transplantation, and a 10% graft loss post switch in those patients switched at 50 days post-transplantation. Thus, the authors concluded that conversion at least 2 months post-transplantation is usually successful when assessed by short term improvement in renal function, but the risk of graft morbidity is substantial if a conversion is undertaken.[13]

Some protocols, however, use only cyclosporine in immunosuppressive treatment. Chapman and Morris compared two patient groups post-transplantation.[14] One group only received cyclosporine treatment, and the other group received azathioprine-prednisolone treatment. Graft survival was significantly better in the cyclosporine treated group. However, 48% of cyclosporine treated patients required dialysis during the first seven days post-transplantation compared with 31% of azathioprine-

prednisolone treated patients. Urine output in the first 24 hours post-transplantation indicated that 33% of all cyclosporine patients (67% of those requiring dialysis) passed urine initially, but subsequent dialysis was needed due to allograft dysfunction. Also, 16% of cyclosporine patients did not pass urine in the initial period following transplantation. Thus, cyclosporine patients required dialysis in the first week post-transplantation more than azathioprine-prednisolone patients due to post-transplantation occurrences such as nephrotoxicity, and not directly due to donor variables.[14] Serum creatinine concentration was also found to be significantly higher in the cyclosporine treated group when compared to the azathioprine-prednisolone patients, until a switch from cyclosporine to azathioprine-prednisolone occurred. The conversion caused a slow but progressive decrease in serum creatinine concentration in previously treated cyclosporine patients.[14]

The investigators mentioned thus far have indicated a cyclosporine-prednisone to azathioprine-prednisone switch to be beneficial when attempting to avoid nephrotoxicity, but detrimental and risky when considering the graft losses that occur post-switch. Adu et. al have recently reported the cyclosporine-prednisone to azathioprine-prednisone switch to be very harmful.[15] These investigators studied four patients who were switched at 3 months post-transplantation. Three of the individuals studied

experienced a chronic rejection immediately following the switch, and two of these individuals were returned to cyclosporine treatment. Thus, Adu et. al have indicated that the penalties of rejection and infection following a cyclosporine-prednisolone to azathioprine-prednisolone switch to be unacceptable. These investigators suggest that renal transplant patients remain on a cyclosporine-prednisolone regimen as their primary immunosuppressive therapy used post-transplantation.[15]

The present investigation was performed to investigate patients at Yale-New Haven Hospital who were switched from a cyclosporine-prednisone to an azathioprine-prednisone regimen in order to examine our own experience with this protocol.

PURPOSE

To evaluate the clinical course of cadaveric renal transplant recipients converted from maintenance therapy with cyclosporine-prednisone to azathioprine-prednisone treatment within the first 21 months after transplant, the incidence of acute allograft rejection after the switch as well as renal function and graft survival at 6 months, 1 year, 18 months, 2 years, 30 months, and 3 years were examined.

MATERIALS AND METHODS

PATIENT POPULATION

Cyclosporine was first made available for use at Yale-New Haven Hospital in December 1983. It was initially used only in high risk renal cadaveric recipients. Within 9 months, it was being used in all cadaveric recipients. Most patients originally started on prednisone and cyclosporine were switched to prednisone and azathioprine within 3-21 months post-transplantation to prevent chronic interstitial fibrosis. This policy for cyclosporine use was followed from December 1983 to July 1986. During this time period, 59 cadaveric renal transplants were performed. Of these, 35 were eliminated from evaluation because of early graft loss, death, or failure to be placed on cyclosporine initially following transplantation. This left 24 patients initially started on cyclosporine and maintaining a functional graft 3-21 months post-transplantation. Since most patients were treated similarly, there existed no control population of patients who remained on cyclosporine alone and who were not converted to azathioprine. In the years prior to the introduction of cyclosporine, all cadaveric renal transplant recipients were started and continued on an azathioprine-prednisone protocol. Comparing these patients to the current population would also not represent a meaningful control group since initial graft success is different with cyclosporine compared to azathioprine. Therefore, in this

retrospective analysis, no control group could be used. Rather, each patient served as his or her own control for a rejection and assessment of renal function in the before versus after switch period.

DATA COLLECTED

Twenty-four patients (see Figure 1), all of whom were switched from cyclosporine-prednisone to azathioprine-prednisone, form the basis of the present investigation. In order to determine the effects of the conversion on graft function, graft rejection and graft survival, a retrospective chart review was undertaken. The data collected were obtained from in-patient and out-patient records, laboratory sheets, and the personal files as well as communication with Drs. Margaret Bia, Alan Kliger, Karen Gaudio and Norman Seigel.

Patient characteristics such as age, history of diabetes, prior loss of a kidney graft, and number and severity of rejections prior to conversion were analyzed to see if any of these factors influenced the patient's course post-conversion. Diabetes is taken into special consideration because of its association with poorer patient survival compared to non-diabetics receiving renal transplants. Renal function post-transplantation and post-conversion was assessed according to serum creatinine concentration and blood urea nitrogen (BUN) levels at 6, 12, 24, 30, and 36 months after transplant, and at 6, 12, 18, and 24 months post-conversion. Cyclosporine trough levels were measured by high pressure liquid chromatography (HPLC). The incidence of rejection both before and after the conversion was also evaluated. Rejection was defined as an

increase in serum creatinine concentration responsive to treatment with high intravenous doses of solumedrol. In most cases examined, rejection was confirmed by renal biopsy. Rejection was determined as mild if the patient received solumedrol alone, and severe if they required additional treatment with antilymphocyte globulin (ATG), or OKT3 monoclonal antibodies.

A causal relationship between cyclosporine-azathioprine conversion and a subsequent rejection or graft loss was assessed by noting the time of the conversion, the time post-transplantation that the conversion took place, the time the rejections occurred after the switch, and renal function post-conversion. The amount of overlap of concomitant azathioprine with cyclosporine treatment during each switch was also noted. Patients who rejected or lost their graft post-conversion were compared to those who did not for differences in factors that may have predisposed them to a poor response post-conversion such as the number of rejections before the switch, primary or second transplant, diabetes mellitus, and renal function before the switch.

STATISTICAL ANALYSIS

Statistical analyses of the data were made utilizing life table preparations, Chi-Square analyses, and the Simple T-Tests. All results are presented as the mean $\pm$ the standard deviation of the mean.

RESULTS

THE PATIENT POPULATION

The population of 24 cadaveric recipients evaluated constituted 40.6% of all cadaveric transplants performed and 51% of all cadaveric transplant patients begun on cyclosporine during the 27 month time period indicated (Figure 1). Of the 47 patients initially begun on cyclosporine-prednisone immunosuppressive therapy, 17 patients never reached the time period post-transplantation in which they could be switched because of severe rejection (10 patients), graft loss from technical difficulties (4 patients), or discontinuation of immunosuppression due to infection (3 patients). Six patients reached the switch point but were never switched due to allergic reactions to azathioprine in one patient, loss of follow-up in two patients, deteriorating renal function in one patient, and M.D. philosophy in two patients. Thus, the cyclosporine-prednisone switch patients represent only a fraction of the total number of transplants performed between December 1983 and March 1986. They represent a group of patients initially started on cyclosporine and maintaining a graft survival for three months or more post-transplantation. These patients were followed for a mean of 27.25$\pm$9 months with a range of 13-43 months. Twelve patients were followed 13-24 months, and twelve patients were followed 26-43 months.

ANALYSIS OF PRE-SWITCH CHARACTERISTICS

The background characteristics of all 24 cadaveric renal transplant recipients in the present investigation were examined. Data presented in Table I indicates that the majority of the patients studied were primary cadaveric graft recipients (20 vs 4). Only 7 patients (29%) had diabetes mellitus. Mean creatinine concentration prior to switch was 2.0±0.7 mg/dL with 8 patients having a creatinine concentration ≥2.5 mg/dL. Almost two-thirds of all patients had experienced at least one rejection prior to switching. Four patients had experienced 2 rejections prior to the switch. In 9 of the 15 patients that suffered a rejection prior to the switch, the rejection was severe requiring ATG or OKT3 after pulse steroid treatment. Most patients (83%) were switched because of protocol to avoid future nephrotoxicity. Only 4 patients (17%) were perceived as being nephrotoxic as the immediate reason for the switch. Most patients were switched by overlap which consisted of a concomitant administration of azathioprine and cyclosporine for a period of 5-7 days in which the cyclosporine trough level value in the patient population at the time of the switch was within the therapeutic range of 50-150 ng/ml as measured by high pressure liquid chromatography (HPLC). Patients were switched from a cyclosporine dose of 12.6±6.0 mg/kg/day to an azathioprine dose of 2.0±0.35 mg/kg/day.

Figure 2 illustrates the distribution of the 24 patients studied concerning the time of the immunosuppressive switch post-transplantation. Seventy-five percent of the 24 patients studied switched immunosuppressive therapy between 2.75 and 7 months post-transplantation. Fourteen patients (58%) were switched at 6 months or greater than 6 months post-transplantation, and 2 patients were switched after 11 months post-transplantation.

ANALYSIS OF RESPONSE TO SWITCH: REJECTION

Ten patients (42%) had an acute rejection at some point following the switch from cyclosporine to azathioprine. In eight of the ten patients (80%) the rejection was mild and occurred only once. One patient suffered a single severe rejection, and one patient suffered both a mild and severe rejection following the switch. Eighty percent of these rejections occurred between 1 week and 7 months post-switch. Three patients had more than one rejection post-switch. Three rejections occurred less than 1 month post-switch and 4 rejections (40%) occurred within 3 months post-switch (Table II). All patients responded to rejection treatment in which their rejection was resolved except for the one patient, X.X., that suffered a severe rejection post-switch. This patient ultimately lost her graft due to her inability to resolve the rejection.

Factors were compared in the 10 patients with a rejection post-switch versus the 14 without to determine if any characteristic was associated with a risk for rejection post-switch. The frequency of these characteristics was compared by the Fisher's Exact Test. As seen in Table III, there was no difference between the groups in age, sex, race, presence of diabetes mellitus, presence of a rejection before switch, time of switch or renal function before the switch. There was also no relationship (by linear regression analysis) of the number of rejections before the

switch and the number of rejections following the switch. Thus, there was no characteristic or factor which was associated with an increased frequency of rejection post-switch.

Analyzed in another way, mean patient age, mean time of switch post-transplantation and mean renal function at the time of the switch were compared in patients with versus patients without a rejection post-switch (Table IV). As seen in Table IV, these variables were nearly identical in the 10 patients experiencing a rejection post-switch compared to the 14 patients free of a rejection after the switch.

RESPONSE TO SWITCH: RENAL FUNCTION

To assess graft function, creatinine concentrations at 6, 12, 18, 24, 30, 36 and greater than 36 months post-transplantation and post-switch were examined in the 24 cadaveric renal transplant patients as a whole. Renal function was also compared in patients who experienced a rejection post-switch and those who did not. Figure 3 illustrates the mean creatinine concentration values at various intervals post-transplantation for the patient population as a whole. Renal function was well preserved in most patients except for 3 patients whose creatinine concentration values rose above 3.0 mg/dL at 2 years post-transplant. The mean serum creatinine concentration at 2 years post-transplantation for the group as a whole was 2.3 ± 1.0 mg/dL.

Renal function was compared in patients who suffered no rejections of any kind post-switch and in those who experienced a post-switch rejection (Figures 4 & 5). There was a tendency for serum creatinine concentrations to be higher in patients who suffered a rejection post-switch, but the difference did not reach statistical significance (by Student's T-Test), The tendency toward a higher mean creatinine at year 2 in the rejection group is attributable to the 3 patients with serum creatinine values of 3.2, 4.0, and 4.9 mg/dL.

These three patients clearly did not benefit from the immunosuppressive switch. Patient X.X. was switched 5 months post-transplantation and suffered one rejection prior to the switch. This patient suffered a severe rejection after which normal renal function was never restored and she ultimately lost the graft at 28 months post-switch. The pattern of her graft loss was most consistent with a chronic rejection process. The second patient with markedly impaired graft function post-switch, Y.Y., suffered two rejections following the switch at 19 and 20 months post-transplantation, respectively. Patient Y.Y. was switched from cyclosporine to azathioprine at 4 months post-transplantation. This patient had also suffered a severe rejection prior to the switch and had a serum creatinine concentration of 8.9 mg/dL at the conclusion of this study. Patient Y.Y. eventually started dialysis treatment four months after this study was completed. The last patient to exhibit serum creatinine concentrations 3.0 mg/dL post-switch, Z.Z., also eventually lost his graft at 31 months post-transplantation. Patient Z.Z. had suffered 1 severe rejection prior to the switch, and a mild and severe rejection following the switch. The first of these two rejections occurred 1 week post-switch, the second at two months post-switch. These rejections were resolved which leads one to suspect that the eventual graft loss that occurred at 31 months post-transplantation was due to a chronic rejection process.

When one analyzes mean serum creatinine concentration values in the time interval after switching (not time post-transplantation seen in Figure 5) in rejectors versus post-switch non-rejectors, there is a tendency for serum creatinine concentrations to be higher in patients with a rejection, but the difference fails to reach statistical significance (Figures 6 & 7). There was also a tendency for creatinine concentrations to fall after the switch to azathioprine, a tendency that was more obvious in patients without a rejection. This tendency was apparent by the first month post-switch.

Individual serum creatinine concentrations for post-switch rejectors and non-rejectors illustrates that the post-switch rejectors display deteriorating renal function at successive time intervals post-transplantation (Figures 8a and 8b). After 12 months post-transplantation, 11 out of 14 (79%) post-switch non-rejectors had serum creatinine values $\leq$2.0 mg/dL. This is in sharp contrast to the patients experiencing rejection post-switch in which only 5 out of 10 (50%) patients had a creatinine $\leq$2.0 mg/dL after 12 months post-transplantation.

RESPONSE TO SWITCH: GRAFT SURVIVAL

Cumulative survival data is presented in life tables in Figures 9 and 10. Figure 9 presents actuarial patient survival. One year patient survival was 100%. Two and three year patient survival dropped to 79% due to the death of three patients between 1 and 2 years. One patient, A.A., a severe alcoholic, died at 20 months post-transplantation due to severe pneumonia and expired with a functioning graft. The second patient, B.B., died at 24 months following transplantation due to a massive myocardial infarction with chronic sepsis due to a liver abscess. This patient's death was unrelated to the kidney graft. The third patient, C.C., expired at 2 years post-transplantation due to severe gastrointestinal bleeding. This patient had lost her kidney graft at 18 months post-transplantation and died while receiving dialysis treatment.

Actuarial one year graft survival was 100% (Figure 10). At two years, graft survival decreased to 79.5% due to the loss of 4 grafts: 3 losses due to patient death, and 1 loss due to a chronic rejection. At 36 months, graft survival decreased again to 58% due to the loss of two more grafts due to chronic rejection.

Looking at the patient population as a whole, 3 patients (12%), experienced graft loss at 18 to 33 months post-transplantation. The frequency of patients that experienced a graft loss following the immunosuppressive

switch was 12%. Finally, the incidence of rejection was 42% in the population of patients studied.

DISCUSSION

This study was performed to analyze the safety and efficacy of switching transplant patients from cyclosporine to azathioprine. A switch from cyclosporine-prednisone to azathioprine-prednisone would avoid the long-term nephrotoxic effect of cyclosporine along with its cost, hirsutism side effect and a multitude of other problems. Do patients benefit if such a switch is undertaken? This is the basic question that the present investigation set out to evaluate. Since 42% of the patients that do switch immunosuppressive therapy suffer a rejection following the switch (occurring at 6 months to 33 months post-transplantation), it may seem risky to switch. If, however, one appreciates that acute cellular mild rejections accounted for 90% of these rejections then such an immunosuppressive switch may not appear to be a life threatening or graft threatening procedure, despite the potential for rejection which follows.

Eighty percent of these post-switch rejections occurred between 1 week and 7 months post-switch with 30% occurring at 1 week post-switch (Table II). It seems likely that the switch can be implicated in rejections occurring within one week of the switch. The three patients that rejected at 1 week post-switch were at 6, 7, and 9 months post-transplantation. This is an unusual time to have a spontaneous rejection, and it makes it likely that the

rejection was related to the switch.[16] It is less clear whether the rejections occurring after this period are related to the switch. Patients rejecting 3.5-28 months after the switch are probably experiencing rejection at a higher frequency than would be expected 19 to 33 months post-transplantation, but without a control group of patients maintained on cyclosporine, this is difficult to analyze.

Shen et. al studied 37 patients who were switched from cyclosporine-prednisone to azathioprine-prednisone immunosuppressive therapy at 6 months post-transplantation.[17] These investigators found that the 8/37 (22%) rejections that occurred following the switch were 1-3 months following the switch and are therefore likely to have been linked to the switch. They concluded that there is an increased risk of acute rejection following the conversion. A high post-switch rejection frequency was also observed by Vanrenterghem et. al.[18] These investigators switched 9 patients at one month post-transplantation and 9 patients at 3 months post-transplantation. Data obtained indicated that 90% of patients switched at 1 month post-transplantation suffered an acute cellular rejection at 1 week post-switch.[18] If patients were switched at 3 months post-transplantation, the rejection rate declined to 78% but was still high. Thus, it was concluded that an immunosuppressive switch was associated with a high incidence of acute cellular rejection immediately following

the switch.[18] These authors then proposed that maintaining patients on lower doses of cyclosporine would avoid the nephrotoxic effects of cyclosporine on the kidney without compromising graft acceptance. Milford et. al have reported similar results concerning switch data.[19] Fifteen of fifty-two patients switched from cyclosporine to azathioprine (28%) between 4 and 6 months post-transplantation experienced acute cellular rejection after the switch which was, however, easily controlled. These investigators conclude that the conversion is possible, but not risk free to the patient and the graft.

Data from Shen, Vanrenterghem and Milford clearly suggest that switching from cyclosporine to azathioprine too early post-transplantation may be associated with acute rejection, but in the present study no relationship was found between the time of switch post-transplantation and the frequency of rejection post-switch. Our failure to document a correlation may be due to the small numbers evaluated. Our frequency of post-switch rejection was similar to that described by Shen and Milford, but lower than that described by Vanrenterghem.

Concerning renal function in these patients, the patient population as a whole maintained a stable serum creatinine concentration under 2 mg/dL up to 18 months post-transplantation (Figure 3). The mean values tend to increase after this time interval, but this is mainly due to

one patient, Y.Y., whose deteriorating renal function affected the mean value of the decreasing sample size considerably. There was a general tendency for serum creatinine concentrations to decrease following the switch. These data suggest that the switching may improve renal function in most transplant patients. Patients experiencing a rejection post-switch were more likely to experience a deterioration in renal function (Figure 8b). Renal function deteriorated in an additional 3 patients even though no post-switch rejection occurred (Figure 8a). Again, without a control group remaining on cyclosporine, it is difficult to know whether this loss of graft function is greater than what would have occurred had the patients remained on cyclosporine.

Discussing the results of Shen et. al once more, these investigators found that the initial response to the switch was a 24% decrease in serum creatinine concentration values and therefore an improvement in renal function.[17] This improvement, however, was only seen in patients who did not suffer an acute cellular rejection following the immunosuppressive switch.[17] Similar results have been reported by Milford et. al. In this investigation previously described, 52 patients were switched from cyclosporine to azathioprine 4-6 months following transplantation. Fifty of these 52 patients (96%) maintained functioning grafts and experienced a 20% mean

reduction in their serum creatinine concentrations over a 9 to 22 months time period.

Further studies by Maddux et. al also demonstrate a substantial decrease in serum creatinine concentration values post-switch.[20] In this investigation, 21 patients were switched from cyclosporine to azathioprine between 2 weeks and 9 months post-transplantation. Renal function was significantly improved ($p<0.05$) at 6 months post-switch when compared with pre-switch serum creatinine concentration values. All patients switched experienced an improvement in renal function. These investigators also found no difference in the rate of rejection in switched patients when compared with non-switched matched controls. They conclude that the switch is safe and improves renal function. In our study we also observed a trend for creatinine concentrations to decrease following the switch to azathioprine, but the trend was apparent only in patients not experiencing a rejection (Figures 6 & 8a).

One year patient survival in the population was 100% in the present investigation. It dropped to 79% at 2 years due to the deaths of three patients from infection and gastrointestinal bleeding and remained at 79% at 3 years. Graft survival was also excellent (100% at 1 year and 79.5% at two years) but fell to 58% at 3 years (Figures 9 & 10). These grafts were all lost due to acute or chronic rejection after the switch. Veitch et. al report an actuarial 2 year

graft survival of 73% in a group of 42 patients converted from cyclosporine to azathioprine at 3 months post-transplantation.[21] Similar results have been demonstrated by Tegzess et. al who converted 37 cadaveric renal transplant patients from cyclosporine to azathioprine at 4 months post-transplantation.[22] These researchers initially used cyclosporine alone in their graft recipients, thus observing the direct effects of cyclosporine on the kidney. An actuarial graft survival 94% at 1 year, 80% at 2 years, and 75% at 3 years post-transplantation.[21] Grafts were lost due to rejection episodes. Although no control group was followed in this study, these results compare favorably to the 1 and 5 year follow-up of patients maintained on cyclosporine. Studies of 1 and 5 year graft survival in patients maintained on cyclosporine are 84% and 97% one year graft and patient survival, respectively.[23] This dropped to 67% and 92% at 3-5 years post-transplantation.[22] These researchers report that nephrotoxicity was the only persistent long term complication of cyclosporine use.

Although graft survival in the present investigation compares favorably with that described in patients maintained on cyclosporine at 2 to 3 years post-transplantation, the incidence of rejection is higher than expected 3-21 months post-transplantation.[16] When all the results are viewed together, it can be seen that 37.5% of patients either experience a rejection and/or deteriorating renal function (creatinine >2.0 mg/dL) post-switch. The

data therefore suggests that the immunosuppressive switch should be considered with caution. However, since the current data has observed a similar graft survival as that described with cyclosporine, the question still remains whether long-term graft survival and graft function will be better preserved in patients switched versus those maintained on cyclosporine in whom chronic nephrotoxicity might occur.

SUMMARY

1. Graft survival in patients switched from cyclosporine to azathioprine compares favorably with other studies in which patients were maintained on cyclosporine as described.

2. 42% of patients experience a rejection post-switch which is usually mild but occurring later in the post-transplant period than expected, making a causal relationship with switch seem likely.

3. Although rejections were usually mild, 3 patients experiencing rejection post-switch eventually lost their grafts.

4. Serum creatinine concentration values post-switch remained stable or decreased in 12 patients but deteriorated in 6 patients. Four patients suffered rejection (2 patients expired).

5. Improvement in renal function was especially evident in those patients who did not suffer a rejection post-switch.

CONCLUSION

The present investigation has demonstrated that following renal transplantation, an immunosuppressive switch from cyclosporine-prednisone to azathioprine-prednisone is accompanied by both advantages and disadvantages. Thus, the immunosuppressive switch cannot be undertaken without caution. The author of the present investigation believes that an alternative to an immunosuppressive switch exists which will avert the nephrotoxic effects of cyclosporine on the kidney and maintain adequate immunosuppression.

Triple therapy involving cyclosporine, prednisone and azathioprine now appears to be the solution to the problem of cyclosporine nephrotoxicity, avoiding acute cellular rejection following the immunosuppressive switch, and maintaining allograft acceptance in the renal transplant individual. Lorber et. al have studied the effects of an immunosuppressive triple therapy regimen upon renal allograft acceptance and serum creatinine concentrations following transplantation.[24] Fourteen patients, eleven of whom were cadaveric renal transplant recipients, were treated with cyclosporine-prednisone following transplantation. These patients displayed a continued elevation in serum creatinine concentration values greater than 2.5 mg/dL up to 246$\pm$100 days post-transplantation. The method of initiation of azathioprine therapy in addition to cyclosporine-prednisone therapy involved the introduction of

azathioprine over a 5-7 day period to a final dose of 2 mg/kg/d.[23] Once the azathioprine dose was achieved, cyclosporine doses were reduced in 50-100 mg/d until a final dose of 2.5-3 mg/kg/d was reached. The results of the cyclosporine dose reduction were encouraging. None of the 14 patients on triple therapy suffered any adverse effects to the therapy, none of the patients suffered acute allograft rejection, and renal function was improved as indicated by decreased serum creatinine concentration values.[23] It was observed that serum creatinine concentration values decreased in accordance with the decrease in the cyclosporine dose over the 5-7 day period. The mean serum creatinine concentration value immediately preceding the reduction in cyclosporine was 3.7 ± 0.7 mg/dL, whereas at 120 days following the initiation of triple therapy, the mean serum creatinine concentration value was reported to be 2.5 ± 0.4 mg/dL.[23] Thus, it is evident that a reduction in cyclosporine doses also reduces the nephrotoxic effects of cyclosporine upon the kidney without sacrificing adequate immunosuppressive therapy.

TABLE I

BACKGROUND DATA FOR 24 RENAL CADAVERIC TRANSPLANT RECIPIENTS BEFORE THE CYCLOSPORINE-PREDNISONE TO AZATHIOPRINE-PREDNISONE IMMUNOSUPPRESSIVE CONVERSION

CHARACTERISTIC	MEAN VALUE or NUMBER OF SUBJECTS	RANGE
CADAVERIC	24 (100%)	
AGE AT TRANSPLANT(yrs)	44.5±13.4	9-64
LENGTH FOLLOW-UP(mo)	27.25±9	13-43
DIABETIC vs. NON-DIABETIC	7 (29%) vs. 17 (71%)	
PRIMARY vs. SECOND GRAFT	20 (83%) vs. 4 (17%)	
CREATININE CONC.≤1mo BEFORE SWITCH (mg/dL)	2.0±0.7	0.7-0.2
NO. OF PATIENTS WITH ≥1 REJECTION BEFORE SWITCH	15	
TIME SWITCH POST-TPX(mo)	6.7±3.7	2.75-21
REASON FOR SWITCH: PROTOCOL vs. NEPHROTOXICITY	20 (83%) vs. 4 (17%)	
PROTOCOL OF SWITCH*: OVERLAP vs. IMMEDIATE	19 (79%) vs. 5 (21%)	
CYCLOSPORINE DOSE SWITCHED FROM (mg/kg/d)	12.7±6	5.1-30
PREDNISONE DOSE SWITCHED FROM (mg/kg/d)	0.25±0.163	0.15-1.0
AZATHIOPRINE DOSE SWITCHED TO (mg/kg/d)	2.0±0.35	1.6-3.0
CYCLOSPORINE TROUGH LEVEL IMMEDIATELY PRECEDING SWITCH (ng/ml)	58±23	18-96

*Overlap= 5-7 days of Azathioprine with Cyclosporine

TABLE II

REJECTION DATA IN THE 10/24 PATIENTS THAT REJECTED POST-SWITCH

PTS	No. REJECTIONS POST-SWITCH	SEVERITY of REJECTIONS POST-SWITCH	TIME TO 1st REJECTION POST SWITCH (mo)*	TIME TO 1st REJECTION POST TRANSPLANT (mo)**
D.D.	1	MILD	1 week	6
Y.Y.	2	MILD	3.5	19
F.F.	1	MILD	15	21
G.G.	1	MILD	7	10
X.X.	1	SEVERE	28	33
Z.Z.	2	MILD, SEVERE	1 week	7
H.H.	1	MILD	6	14
A.A.	1	MILD	5	16
J.J.	2	MILD	2	9
K.K.	1	MILD	1 week	9

*Mean Interval Post-Switch in Which The First Rejection Occurred= 6.8±8.7 months.

**Mean Interval Post-Transplantation in Which The First Rejection Occurred= 14±7 months.

TABLE III

RESULTS OF ANALYSIS OF THE FREQUENCY OF CHARACTERISTICS IN PATIENTS WHO REJECTED vs. THOSE WHO DID NOT FOLLOWING THE IMMUNOSUPPRESSIVE SWITCH

CHARACTERISTIC	FREQUENCY	P VALUE*
AGE:		
≤20 yrs vs. >20 yrs at Transplant	1 vs. 23	NS
≤40 yrs vs. >40 yrs at Transplant	8 vs. 16	NS
≤50 yrs vs. >50 yrs at Transplant	16 vs. 8	NS
≤60 yrs vs. >60 yrs at Transplant	21 vs. 3	NS
Diabetes vs. No Diabetes at Transplant	7 vs. 17	NS
Any Rejection Before Switch vs. No Rejection Before Switch	15 vs. 9	NS
SWITCH:		
≤4 mo vs. >4 mo Post-Transplant	5 vs. 19	NS
≤6 mo vs. >6 mo Post-Transplant	12 vs. 12	NS
≤8 mo vs. >8 mo Post-Transplant	20 vs. 4	NS
≤12 mo vs. >12 mo Post-Transplant	23 vs. 1	NS
CREATININE (mg/dL):		
≤1.0 vs. >1.0 1mo Before Switch	1 vs. 23	NS
≤1.5 vs. >1.5 1mo Before Switch	9 vs. 15	NS
≤2.0 vs. >2.0 1mo Before Switch	15 vs. 9	NS
Male vs. Female	14 vs. 10	NS
White vs. Black	22 vs. 2	NS
Primary vs. Second Transplant	20 vs. 4	NS

Values analyzed using Fisher's Exact Test

* NS denotes not significant

TABLE IV

FREQUENCY OF CHARACTERISTICS IN THOSE PATIENTS WHO REJECTED POST-SWITCH vs. THOSE WHO DID NOT REJECT POST-SWITCH

	REJECTORS N=10	NON-REJECTORS N=14	P VALUE*
CHARACTERISTIC:			
REJECTION INCIDENCE PRE-SWITCH	1.0±0.7	0.7±0.7	NS
TIME OF SWITCH POST-TRANSPLANTATION	6.5±2.4 mo	7±4.4 mo	NS
CREATININE CONCENTRATION IMMEDIATELY PRECEDING SWITCH	2.0±1.0 mg/dL	2.0±0.6 mg/dL	NS

Values analyzed using the Student's T-Test

* NS denotes not significant

FIGURE 1

Breakdown of the patient population. Six patients were never switched due to allergic reaction (n=1), deteriorating renal function (n=1), M.D. philosophy (n=2), and a loss to follow-up (n=2). Switch patients represent only a fraction of the total: 40% of cadaveric transplants, 51% of patients started on cyclosporine, and 28.5% of all transplant patients during this time period.

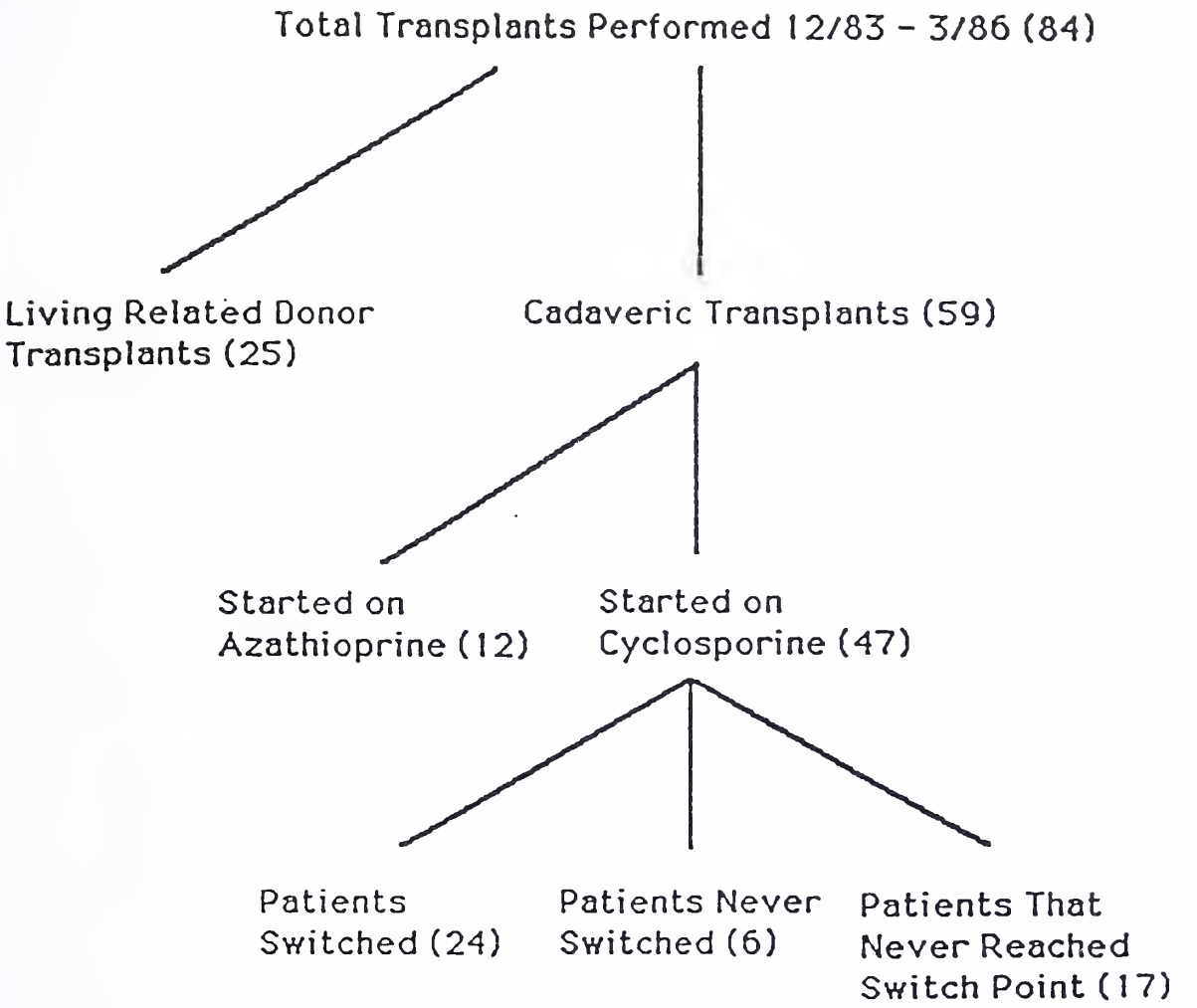

Total Transplants Performed 12/83 - 3/86 (84)
Living Related Donor Transplants (25)
Cadaveric Transplants (59)
Started on Azathioprine (12)
Started on Cyclosporine (47)
Patients Switched (24)
Patients Never Switched (6)
Patients That Never Reached Switch Point (17)

FIGURE 1

FIGURE 2

The number of patients switched at various times post-transplantation is shown here. It is seen that 66% of patients were switched between 4 and 7 months post-transplantation. Twenty-five percent of patients switched between 8 and 21 months post-transplantation.

FIGURE 2

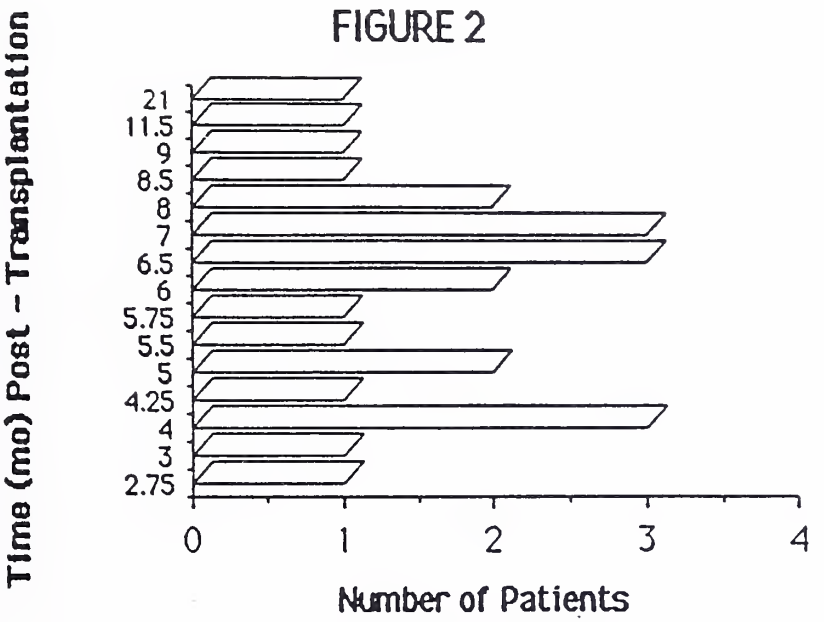

Time (mo) Post - Transplantation
21
11.5
9
8.5
8
7
6.5
6
5.75
5.5
5
4.25
4
3
2.75
0
1
2
3
4
Number of Patients

FIGURE 3

Figure 3 illustrates the mean serum creatinine concentrations (mg/dl) post-transplantation in the patient population as a whole. The open bars represent the mean serum creatinine concentration values, whereas the standard deviations below and above the mean are represented by the open squares and open diamonds, respectively.

Figure 3

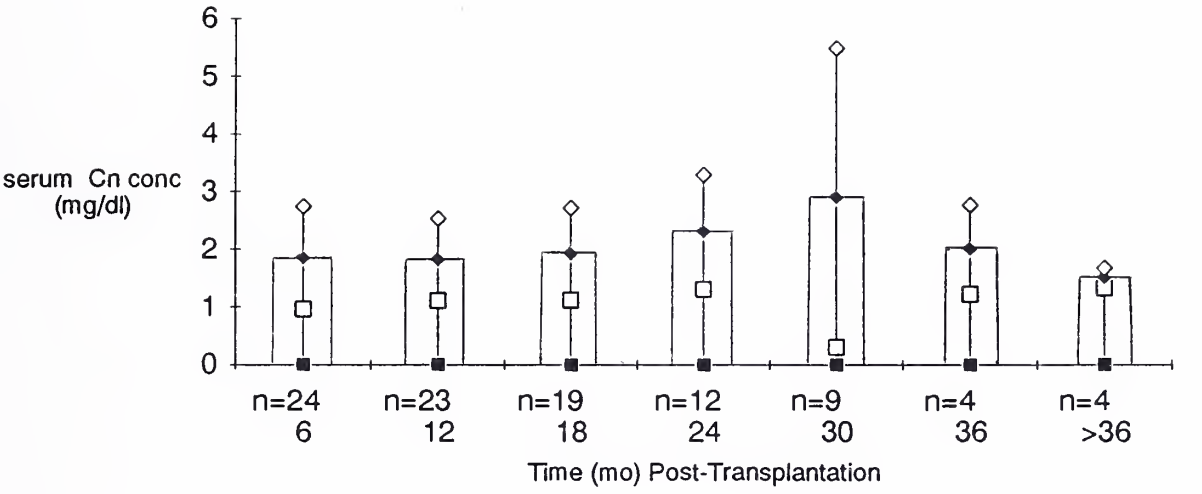

serum Cn conc
(mg/dl)
6
5
4
3
2
1
0
n=24
6
n=23
12
n=19
18
n=12
24
n=9
30
n=4
36
n=4
>36
Time (mo) Post-Transplantation

FIGURE 4

Figure 4 illustrates the mean serum creatinine concentrations (mg/dl) at various times post-transplantation in those patients who suffered a post-switch rejection. Mean values are represented by the open bars, whereas the standard deviations below and above the mean are represented by open squares and open diamonds, respectively.

Figure 4

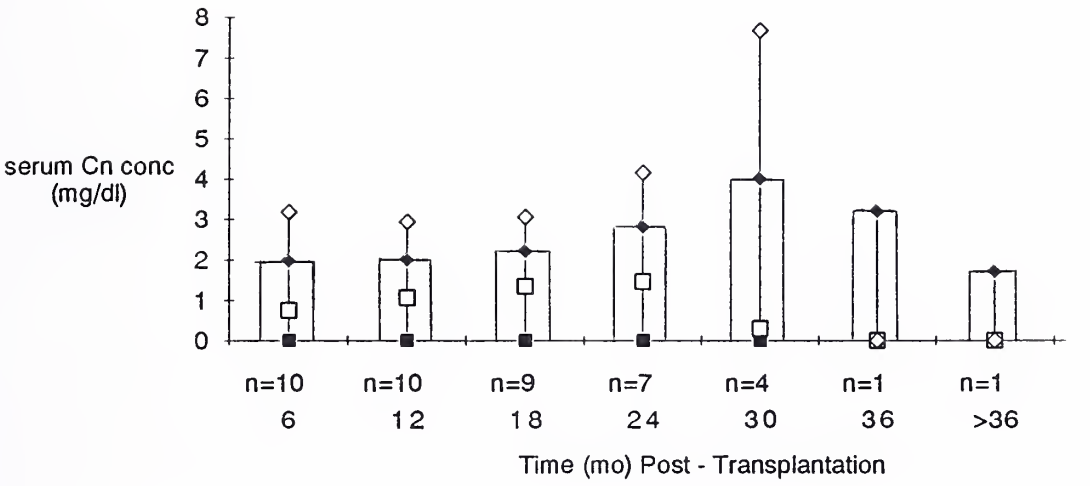

serum Cn conc
(mg/dl)
8
7
6
5
4
3
2
1
0
n=10
6
n=10
12
n=9
18
n=7
24
n=4
30
n=1
36
n=1
>36
Time (mo) Post - Transplantation

FIGURE 5

Figure 5 illustrates the mean serum creatinine concentrations (mg/dl) at various times post-transplantation in those patients who did NOT suffer a post-switch rejection. Mean values are represented by the open bars, whereas the standard deviations below and above the mean are represented by the open squares and open diamonds, respectively.

Figure 5

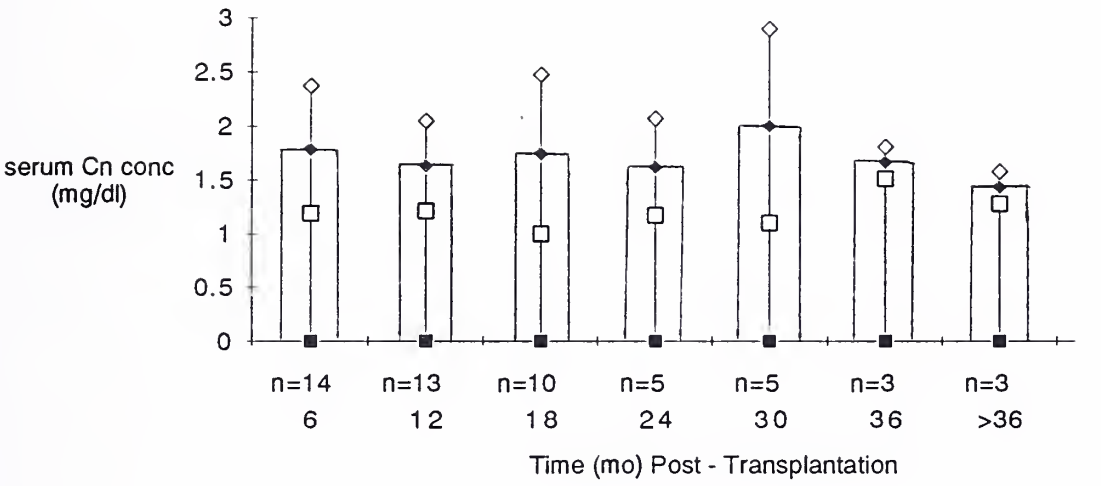

serum Cn conc
(mg/dl)
3
2.5
2
1.5
1
0.5
0
n=14
6
n=13
12
n=10
18
n=5
24
n=5
30
n=3
36
n=3
>36
Time (mo) Post - Transplantation

FIGURE 6

Figure 6 illustrates the mean serum creatinine concentrations (mg/dl) after switching from cyclosporine to azathioprine in patients who did not suffer a post-switch rejection. The first bar represents the mean pre-switch creatinine concentration 1 month pre-switch. Open bars represent mean values, and open squares and open diamonds represent values below and above the mean, respectively.

Figure 6

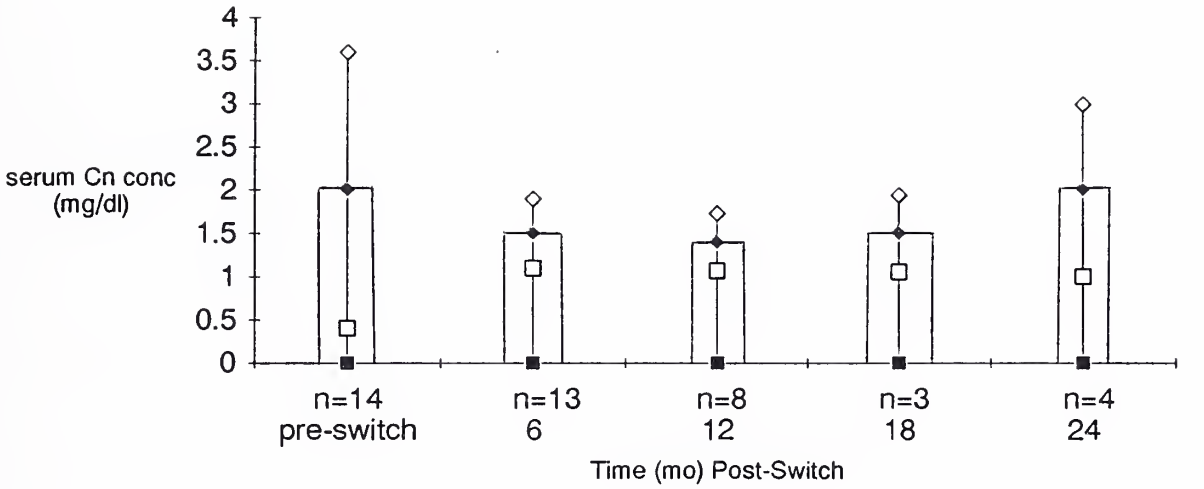

serum Cn conc
(mg/dl)
4
3.5
3
2.5
2
1.5
1
0.5
0
n=14
pre-switch
n=13
6
n=8
12
n=3
18
n=4
24
Time (mo) Post-Switch

FIGURE 7

Figure 7 illustrates the mean serum creatinine concentrations (mg/dl) in patients who suffered at least one post-switch rejection. The first bar represents the mean pre-switch creatinine concentration 1 month pre-switch. Open bars represent mean values, and open squares and open diamonds represent values below and above the mean, respectively.

Figure 7

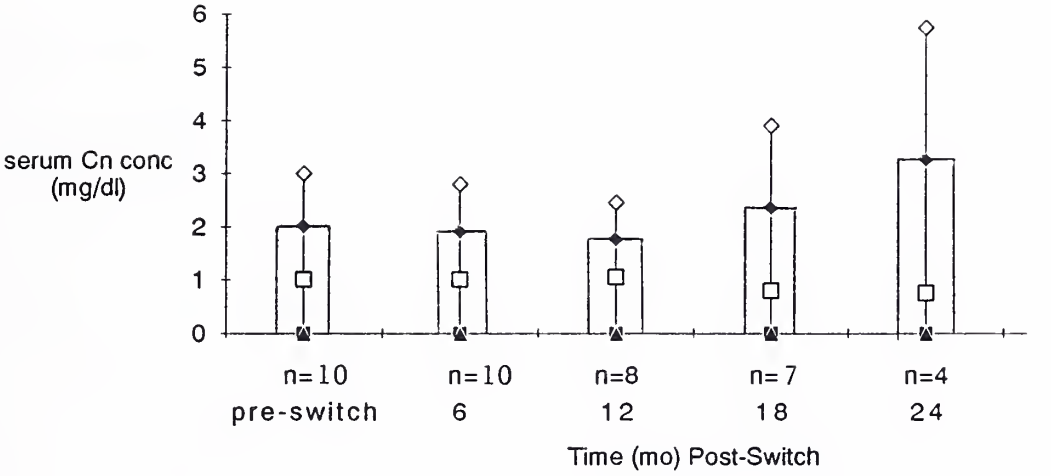

serum Cn conc
(mg/dl)
6
5
4
3
2
1
0
n=10
pre-switch
n=10
6
n=8
12
n=7
18
n=4
24
Time (mo) Post-Switch

FIGURE 8a

Figure 8a illustrates the serum creatinine concentration values for the 14 patients that did NOT suffer a post-switch rejection. For each patient, bars from left to right represent 6, 12, 18, 24, 30, 36 and >36 months post-transplantation, respectively. Values are shown for the duration of follow-up.

Figure 8a

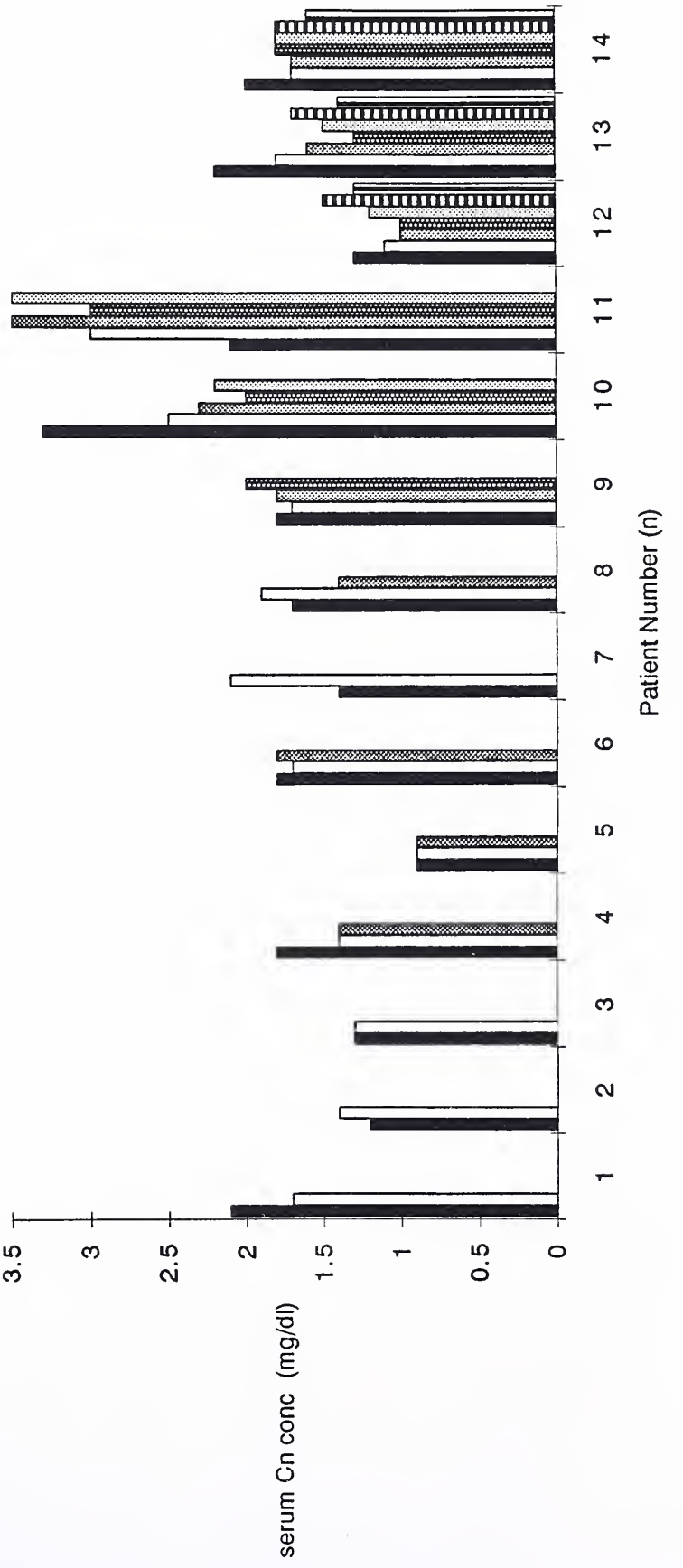

3.5
3
2.5
2
1.5
1
0.5
0
serum Cn conc (mg/dl)
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Patient Number (n)

FIGURE 8b

Figure 8b illustrates the serum creatinine concentration values for each of the 10 patients that did suffer a post-switch rejection. For each patient, bars from left to right represent 6, 12, 18, 24, 30, 36 and >36 months post-transplantation, respectively. Values are shown for the duration of follow-up.

Figure 8b

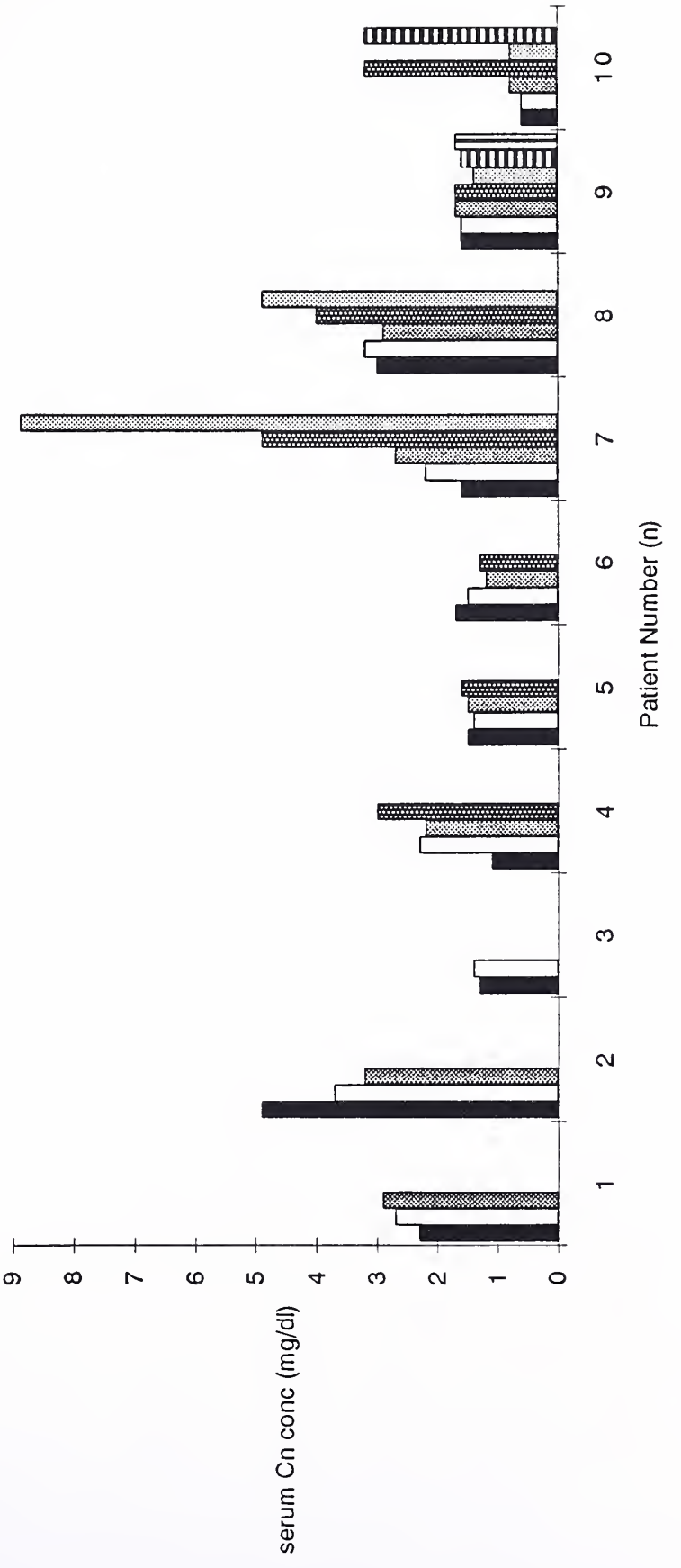

serum Cn conc (mg/dl)
0
1
2
3
4
5
6
7
8
9
Patient Number (n)
1
2
3
4
5
6
7
8
9
10

FIGURE 9

Figure 9 is a life table (actuarial method) representing 1, 2, and 3 year patient survival.

Figure 9

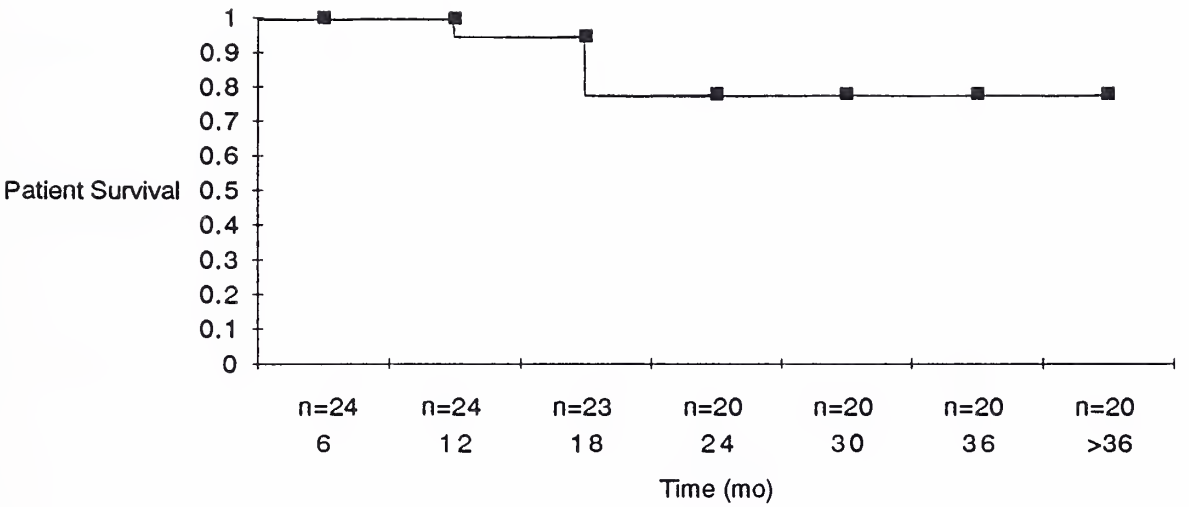
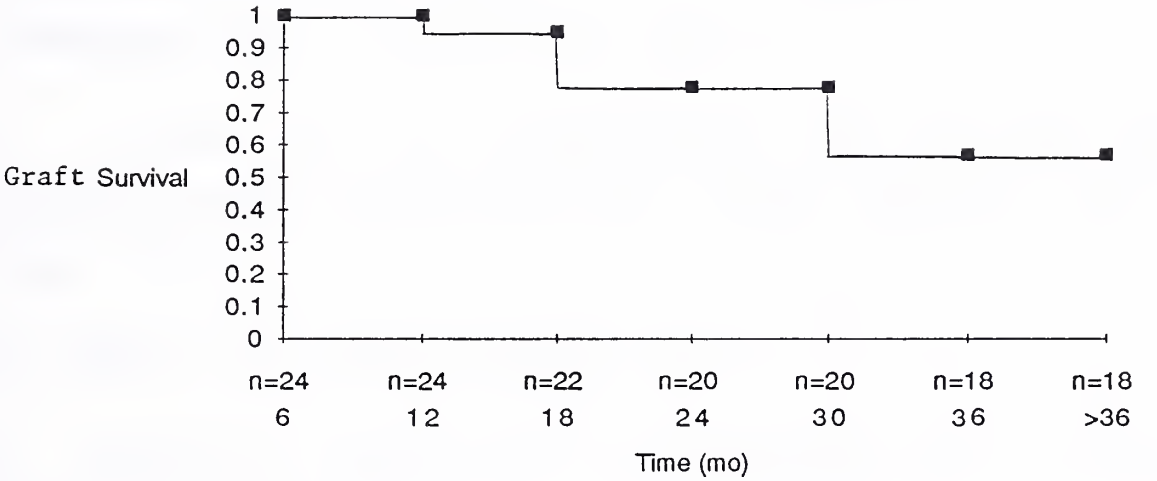

Patient Survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
n=24
6
n=24
12
n=23
18
n=20
24
n=20
30
n=20
36
n=20
>36
Time (mo)

FIGURE 10

Figure 10 is a life table (actuarial method) representing 1, 2 and 3 year graft survival.

Figure 10


Graft Survival
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
n=24
6
n=24
12
n=22
18
n=20
24
n=20
30
n=18
36
n=18
>36
Time (mo)

1. Myers, B.D., Ross, J., Newton, L., Luetscher, J., Perlroth, M., (1984) Cyclosporine-Associated Chronic Nephropathy. N. Engl. J. Med.. 311:699-705.

2. Ferguson, R.M. and Fidelus-Gort, R. (1983) The Immunosuppressive Action of Cyclosporine In Man. Transplant Proc.. 15:2350-2356, Suppl. 1.

3. Lafferty, K.J., Borel, J.F., and Hodgkin, P. (1983) Cyclosporine-A (CsA): Models for the Mechanism of Action. Transplant Proc.. 15:2242-2247, Suppl. 1.

4. Janeway Jr., C.A. Immunobiology: The Cellular and Molecular Basis of the Specific Immune Response, Chpt8, Chpt9, 1987.

5. Borel, J.F. (1981) Triangle. 20:97.

6. Andrus, L., Prowse, S.J., and Lafferty, K.J.. (1981) Scand J Immunol. 13:297.

7. Larsson, E.L.. (1980) Cyclosporine A and Dexamethasone Suppress T-Cell Responses by Selectively Acting at Distinct Sites of the Triggering Process. Journal of Immunology 124:2828-2833.

8. Cohen, D.J., et. al. (1984) Annals of Internal Medicine. 101:667-682.

9. Council on Scientific Affairs. (1987) Introduction to the Management of Immunosuppression. JAMA 257:1781-1785.

10. Hunsicker, L. (1985) Impact of Cyclosporine on Cadaveric Renal Transplantation: A Summary Statement. Am J Kid Dis.

11. Sutherland, D., Fryd, D., Strand, M., Canafax, D., Ascher, N., Payne, W., Simmons, R. and Najarian, J. (1985) Results of the Minnesota Randomized Prospective Trial of Cyclosporine Versus Azathioprine-Antilymphocyte Globulin for Immunosuppression in Renal Allograft Recipients. Am J Kid Dis. 5:318-327.

12. Gonwa, T.A., et. al. (1987) Results of Conversion from Cyclosporine to Azathioprine In Cadaveric Renal Transplantation. Transplantation. 43:225-228.

13. Rocher, L.L. et. al. (1985) Utility of Azathioprine in Management of Renal Allograft Recipients Initially Treated With Cyclosporine. Transplant Proc.. 17:1185-1187.

14. Chapman, J.R., Morris, P.J.. (1985) Cyclosporine Nephrotoxicity and Conversion To Azathioprine. Transplant Proc. 17:254-260.

15. Adu, D., et. al. (1985) Conversion From Cyclosporine to Azathioprine/Prednisolone. Lancet 1:392.

16. Morris, P.J. Kidney Transplantation: Principles and Practice. 1984.

17. Shen, S.Y., Zenal, S.M., Weir, M.R., Dagher, F.J., and Bently, F.R.. (1987) Conversion of Cyclosporine to Azathioprine in Renal Transplant Patients. Transplant Proc.. 19:2032-2036.

18. Vanrenterghem, Y., Waer, M., and Michielsen, P. (1985) A Controlled Trial of One Versus Three Months Cyclosporine and Conversion to Azathioprine in Renal Transplantation. Transplant Proc.. 17:1162-1163.

19. Milford, E.L., Kirkman, R.L., Tilney, N.L., Strom, T.B., and Carpenter, C.B.. (1983) Clinical Experience With Cyclosporine and Azathioprine at Brigham and Women's Hospital. Am J Kid Disease.. 5:313-317.

20. Maddux, M.S., Veremis, S.A., Pollak, R., and Mozes, M.F. (1987) Conversion from Cyclosporine to Azathioprine Improves Renal Function Without Increased Risk of Graft Failure. Transplant Proc.. 19:2007-2009.

21. Veitch, P.S., Taylor, J.D., Feehally, J., Walls, J., and Bell, P.R.F.. (1987) Elective conversion From Cyclosporine to Azathioprine: Long-Term Follow-Up. Transplant Proc.. 19:2017.

22. Tegzess, A.M., van Son, W.J., Beelen, J.M., Sluiter, W.J., Meijer, S., and Slooff, M.J.H.. (1987) Improvement of Renal Function After Conversion From Cyclosporine Only to Prednisolone-Azathioprine Followed by Late-Onset Graft Failure in Renal Transplant Patients. Transplant Proc.. 19:2000-2004.

23. Kahan, B.D., Flechner, S.M., Lorber, M.I., Golden, D., Conley, S., and Van Buren, C.T.. (1987) Complications of Cyclosporine-Prednisone Immunosuppression in 402 Renal Allograft Recipients Exclusively Followed At A Single Center From One To Five Years. Transplantation. 43:197-204.

24. Lorber, M.I., Flechner, S.M., Van Buren, C.T., Kerman, R.H., and Kahan, B.D.. (1985) Cyclosporine, Azathioprine, and Prednisone as Treatment for Cyclosporine-Induced Nephrotoxicity in Renal Transplant Recipients. Transplant Proc.. 17:282-285.

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